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Clinical Picture, Response to Therapy, and Survival of Women With Diffuse Malignant Peritoneal Mesothelioma

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Background and Objectives: The clinical picture, response to therapy, and prognosis of women with diffuse malignant peritoneal mesotheliomas (DMPM) are ill defined. The purpose of this study is to report on the clinical picture, response to therapy, and survival of women with DMPM.
Methods: The study is a retrospective review of 15 women with the confirmed pathologic diagnosis of DMPM treated between 1964 and 1996. Survival curves were constructed according to the Kaplan-Meier method. The effect of different factors on survival was studied using the log-rank test. Two-tailed P values < 0.05 were considered significant.
Results: Clinical features included abdominal distension (11/15, 73%), abdominal pain (6/15, 40%), ascites (9/15, 60%), abdominal or pelvic masses (14/15, 93%), elevated CA-125 (4/4, 100%), thrombocytosis (4/15, 27%), and thrombo-embolic manifestations (3/15, 20%). The response rate to all first-line chemotherapy regimens was 30%. The response rate to paclitaxel/cisplatin was 66.7% and the toxicity was tolerable. The median survival of all patients was 12.5 months. Patients who underwent cytoreductive surgery survived longer than those who underwent biopsy only (median survival 13.5 vs. 6.0 months, $P = 0.24$). Patients who received chemotherapy survived significantly longer than those who did not receive chemotherapy (29.0 vs. 1.0 months, $P = 0.03$). Patients who responded to first-line chemotherapy survived significantly longer than those who did not respond ($P = 0.04$).
Conclusions: Cytoreductive surgery and chemotherapy, especially with paclitaxel and cisplatin, might be of benefit in women with DMPM.
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KEY WORDS: **peritoneal mesothelioma; survival; paclitaxel; cisplatin; cytoreduction**

INTRODUCTION

Malignant mesothelioma is a rare disease with an estimated annual incidence in the United States of 2,200 cases per year [1]. Most malignant mesotheliomas affect the pleura and the incidence is higher in men than in women. Diffuse malignant peritoneal mesotheliomas (DMPM) account for 32% of mesotheliomas affecting women [2]. Pleural and peritoneal mesotheliomas have been reported in association with asbestos exposure. The latency period between exposure and the development of disease may be as long as 40 years [3]. In addition, peritoneal mesothelioma has been reported following radiation therapy [4], mica exposure [5], recurrent peritonitis [6], and administration of thorium dioxide [7].

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TABLE I. Immunohistochemical Differentiation Between Peritoneal Mesothelioma and Peritoneal Adenocarcinoma

Immunohistochemical test	Mesothelioma	Adenocarcinoma
High molecular weight cytokeratin	Positive	Positive or negative
Vimentin	Positive	Positive or negative
Epithelial membrane antigen	Cell membrane is positive	Cytoplasm is positive
B72.3	Positive or negative	Positive
Ber-EP4	Negative	Positive or negative
Leu-M1	Negative	Positive or negative
Mucin	Negative	Positive

TABLE II. Criteria for Diagnosis of DMPM in the Study Group

Pathologic test	No. of patients (%)
H&E-stained sections	15/15 (100)
Immunohistochemical tests	
Positive high molecular weight cytokeratin	15/15 (100)
Positive vimentin	15/15 (100)
Positive epithelial membrane antigen	15/15(100)[a]
Positive B72.3	10/15(66.7)
Negative B72.3	5/15(33.3)
Negative Ber-EP4	15/15 (100)
Negative Leu-M1	15/15 (100)
Negative mucin	15/15 (100)
Electron microscopy	8/8 (100)[b]

[a]Staining was limited to cell membrane.
[b]All were characterized by long slender microvilli. The numerator represents the number of patients whose tumors demonstrate positive or negative test and the denominator represents the number of patients for whom the test was performed based on availability of tissue.

On account of its wide intraperitoneal spread, the clinical presentation and radiologic and operative findings of DMPM in women are similar to those of ovarian and primary peritoneal carcinomas. Surgeons and gynecologists might encounter patients with DMPM when performing exploration for intra-abdominal carcinomatosis.

Although long-term survival has been reported, the prognosis of patients with DMPM is poor with most patients surviving less than 1 year [8]. Reports of the effect of different therapeutic modalities on survival are confounded by the small number of patients, retrospective analysis, inclusion of patients with pleural mesotheliomas, inclusion of patients with both sexes, and lack of well-defined diagnostic criteria. The purpose of the current study is to report on the clinical picture, response to therapy including the results of combined chemotherapy with paclitaxel and cisplatin, survival, and factors that affect survival in women with DMPM.

MATERIALS AND METHODS

A retrospective clinicopathologic analysis of all patients diagnosed with DMPM treated at Roswell Park Cancer Institute between 1964 and 1996 was performed. Cases of mesothelioma involving the peritoneum and the pleura, cases of cystic mesothelioma, well-differentiated papillary mesothelioma, and fibrous mesothelioma were excluded.

Initial diagnosis of DMPM was made by staff at the Division of Pathology at Roswell Park Cancer Institute and confirmed by one of the co-authors (M.E.I.) as part of this study. Confirmation of diagnosis was made using a panel of examination procedures including hematoxylin-eosin (H&E)-stained sections, immunohistochemical testing, and electron microscopy. To differentiate DMPM from peritoneal adenocarcinoma, the following immunohistochemical tests were performed: cytokeratin, vimentin, epithelial membrane antigen, Ber-EP4, Leu-M1, and mucin. Table I demonstrates the immunohistochemical differences between peritoneal adenocarcinoma and mesothelioma and Table II demonstrates the pathological tests performed to confirm the diagnosis of DMPM in our study group. On electron microscopy, mesothelioma is characterized by long slender microvilli.

The medical records of patients with DMPM were reviewed and the following factors recorded: age at diagnosis, race, history of asbestos exposure, history of smoking, presenting symptoms, clinical findings, operative findings and procedures, postoperative therapy including chemotherapy and radiation therapy, response to therapy, date and cause of death. Since there is no adequate staging system for DMPM, the Federation International of Gynecologists and Obstetricians (FIGO) staging system for ovarian cancer was used [9]. Patients were retrospectively staged based on the operation reports and pathological findings. Follow-up was updated until 30 December 1997. Survival was calculated from the date of diagnosis to the date of death or last follow-up. Optimal and suboptimal cytoreduction were defined as cytoreductive surgery resulting in $\leqslant$1.0 cm and >1.0 cm residual tumor, respectively.

Three patients were treated with paclitaxel (135 mg/m^2 over 24 hr) followed by cisplatin (75 mg/m^2) every 4 weeks for a planned treatment of 6 courses. Response to chemotherapy and toxicity were assessed using the World Health Organization criteria [10].

Survival curves were constructed according to the method described by Kaplan and Meier [11] and difference in survival was assessed using the log-rank test [12]. The StatXact statistical software package was used. Two-tailed P values <0.05 were considered statistically significant.

RESULTS

Fifteen women with DMPM were enrolled in the study. These included all women with the confirmed diagnosis of DMPM treated at Roswell Park Cancer Institute between 1964 and 1996. Patient characteristics and presenting clinical features are described in Table III. All

TABLE III. DMPM: Patient Characteristics (N = 15)

Characteristic	N
Race	
White	14
Native American	1
Median age (range), years	63(27–86)
History of asbestos exposure	
Yes	3
No	6
Unknown	6
History of smoking	
Yes	4
No	6
Unknown	5
Symptoms	
Abdominal distension	11
Abdominal pain	6
Postmenopausal bleeding	2
Weight loss	2
Signs	
Ascites	9
Pelvic mass	8
Abdominal mass	6
Pleural effusion	2
Stage[a]	
IIIC	13
IV	2
Thrombocytosis[b]	4
Thrombo-embolic manifestations	3

[a]According to the FIGO staging for ovarian cancer [9].
[b]Platelet count >500,000/ml.

patients had epithelial type of peritoneal mesothelioma. None of the patients was lost to follow-up.

Abdominal distension (11/15, 73%) was the most common presenting symptom and the presence of an abdominal or a pelvic mass (14/15, 93%) was the most common clinical finding. Preoperative CA-125 values were known in 4 patients. All 4 patients had values >35.0 U/ml (38, 342, 633, and 1,003 U/ml). CA-125 values corresponded to the effect of cytoreductive surgery and response to chemotherapy.

The diagnosis in all patients was based on biopsy performed during laparotomy (n = 14) or laparoscopy (n = 1). Preoperative paracentesis was performed in 4 patients and all were reported as adenocarcinoma. Findings at operation included diffuse nodules and plaques involving the peritoneal surfaces and abdominal viscera and large tumor masses involving the upper abdomen and omentum. There was no evidence of hepatic parenchymal involvement or bowel invasion in any of the patients. Two patients had pleural effusion and were staged as stage IV. These 2 patients were judged to have DMPM and not pleural mesothelioma with peritoneal spread based on the findings of computed tomography of the chest, abdomen, and pelvis demonstrating the bulk of the disease to be in the abdomen and pelvis with no obvious pleural involvement.

Frozen-section examinations were described as poorly differentiated adenocarcinoma in 3 of 5 patients in whom

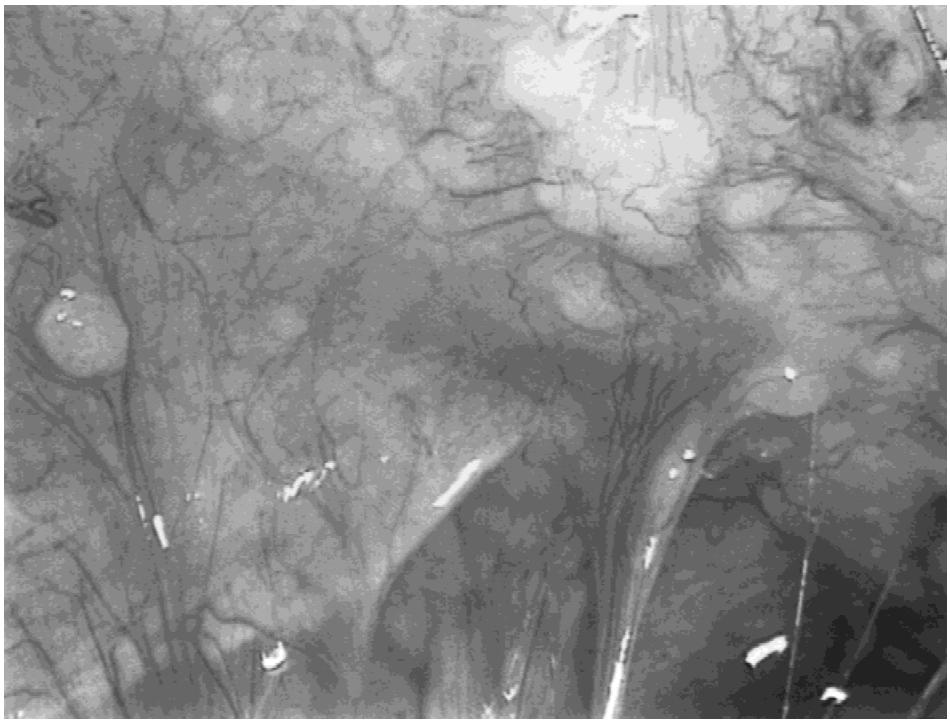

Fig. 1. Laparoscopic appearance of tumor nodules at reassessment laparoscopy in a patient with DMPM following 6 courses of paclitaxel and cisplatin.

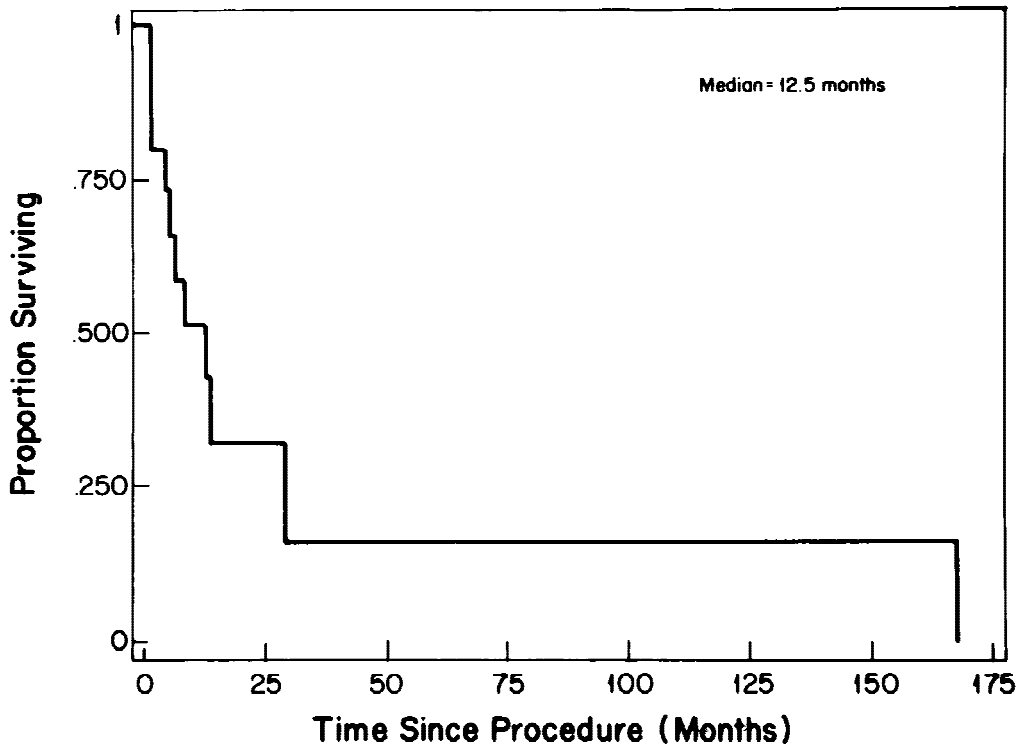

Fig. 2. Overall survival of women with DMPM.

frozen-section biopsy results were known. The other 2 patients were diagnosed as mesothelioma. The surgical procedures performed included biopsy only (n = 6), total abdominal hysterectomy with bilateral salpingo-oophorectomy, omentectomy, and suboptimal (n = 7) or optimal tumor cytoreduction (n = 2). Optimal debulking required extensive surgery and the use of the cavitron ultrasonic aspirator to remove tumor nodules >1.0 cm without bowel resection.

Following surgery, 9 patients received systemic chemotherapy, 1 patient received intraperitoneal chemotherapy with thiotepa, and 5 patients received no further therapy. First-line systemic chemotherapy regimens used included cyclophosphamide and cisplatin (n = 2), doxorubicin (n = 1), dacarbazine (n = 1), cisplatin (n = 1), 5-fluorouracil (n = 1), and paclitaxel and cisplatin (n = 3). Five patients received salvage chemotherapy and one patient received whole abdominal radiation therapy (4,000 cGy) for recurrent disease. Two patients underwent secondary cytoreductive surgery for recurrent disease. Only one patient achieved complete clinical response to the combination paclitaxel and cisplatin and is still alive with no evidence of disease 12.5 months following initial diagnosis. Another patient treated with paclitaxel and cisplatin had partial surgical response on reassessment laparoscopy (Fig. 1) following 6 courses of chemotherapy. The third patient who received paclitaxel and cisplatin demonstrated clinical progression following 2 courses of chemotherapy and underwent secondary cytoreductive surgery. The response rate to first-line paclitaxel and cisplatin was 66.7%. Three of 10 patients (30%) receiving postoperative first-line chemotherapy had partial or complete response to therapy. These included 2 patients receiving paclitaxel and cisplatin and 1 patient receiving intraperitoneal thiotepa. Therapeutic modalities associated with partial clinical response as salvage therapy included radiation therapy (n = 1), doxorubicin (n = 1), dacarbazine (n = 1), and cyclophosphamide and cisplatin (n = 1).

Chemotherapy toxicity was evaluable in 6 patients (2 who received cyclophosphamide and cisplatin, 1 who received cisplatin, and 3 who received paclitaxel and cisplatin. One patient on cyclophosphamide and cisplatin and 2 patients on paclitaxel and cisplatin developed grade 3 neutropenia. All patients who received cyclophosphamide and cisplatin or paclitaxel and cisplatin (n = 5) developed alopecia.

The median overall survival of all patients was 12.5 months (Fig. 2). Five patients survived longer than 1 year and one of these patients survived for 14 years. The longest survivor had documented DMPM based on examination of H&E-stained sections and immunohistochemical examination. Specifically, her tumor stained positive for high molecular weight cytokeratin, vimentin, epithelial membrane antigen (staining limited to cell membrane), and B72, and stained negative for Ber-EP4, Leu-M1, and mucin. She underwent suboptimal cytoreductive surgery, showed partial response to first-line che-

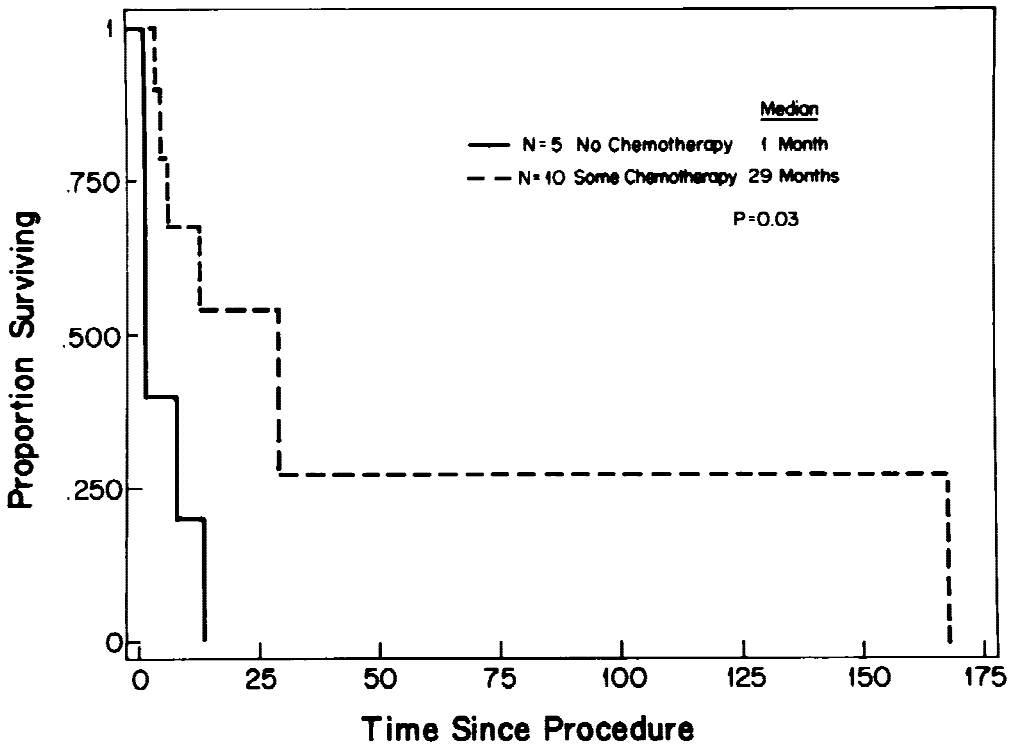

Fig. 3. Survival of women with DMPM according to postoperative therapy.

motherapy with intraperitoneal thiotepa, was later treated with whole abdominal radiation therapy (4,000 cGy) with partial response, had secondary cytoreductive surgery followed by doxorubicin and bleomycin as third-line and methyl-lomustine as fourth-line therapy. At the date of last follow-up (30 December 1997), 11 patients were dead with disease, 1 was alive with no evidence of disease, and 2 were alive with disease and undergoing further chemotherapy.

Survival of patients with DMPM differed according to the extent of the surgical procedure performed. Patients who had biopsy only and no surgical debulking (n = 6) had a median survival of 6.0 months. Patients who underwent operative debulking whether optimal (n = 2) or suboptimal (n = 7) had a median survival of 13.5 months. Due to the small number of patients, the difference in survival was not statistically significant (P = 0.24). There was no difference in the proportion of women who received chemotherapy following either biopsy or cytoreductive surgery (4/6, 66.7% vs. 6/9, 66.7%). However, the 3 women who received paclitaxel and cisplatin had cytoreductive surgery.

There was an apparent survival advantage to the administration of chemotherapy. As demonstrated in Figure 3, the median survival of patients who did not receive chemotherapy (n = 5) was 1.0 months. This was significantly shorter than the median survival of the 10 patients who received chemotherapy (29.0 months, P = 0.03). As demonstrated in Figure 4, response to chemotherapy seemed to significantly affect survival. Patients who showed progression on first-line chemotherapy (n = 7) had a median survival of 12.5 months. Those who responded either completely or partially to first-line chemotherapy (n = 3) survived for 9+, 12.5+, and 168 months. The difference in survival between these 2 groups was statistically significant (P = 0.04).

DISCUSSION

DMPM are rare tumors that present in women with clinical and operative findings indistinguishable from those of advanced stage ovarian and primary peritoneal carcinomas. Moertel [8] noted the characteristic contrast between the massive abdominal involvement and the minimal visceral invasion and metastatic dissemination. As demonstrated by our series, cytologic and frozen-section examinations are often diagnosed as adenocarcinoma. Confirmation of the pathologic diagnosis of DMPM often requires a battery of immunohistochemical staining (Table I) and electron microscopy.

The optimal treatment regimen for DMPM remains to be established. The extent of tumor spread precludes complete surgical resection in most patients. Because these tumors are rare, experience in their chemotherapy is limited. Chemotherapeutic regimens reported to demonstrate response in these patients include cisplatin [13,14], doxorubicin [15,16], and intraperitoneal chemotherapy [17]. Our report is the first to describe the effi-

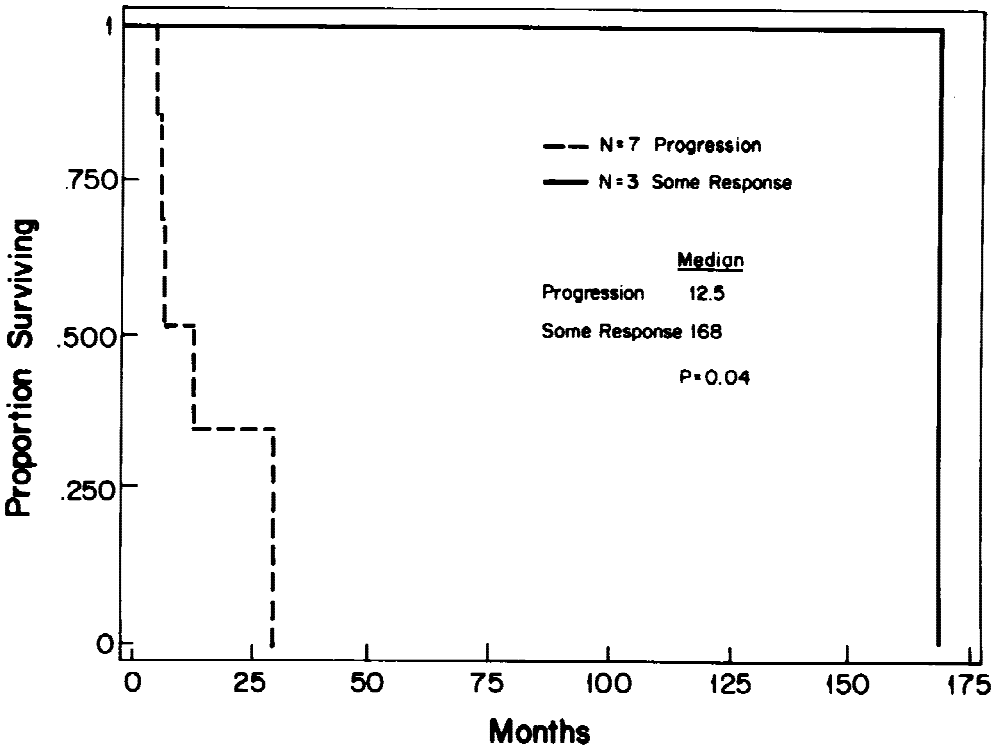

Fig. 4. Survival of women with DMPM according to response to first-line chemotherapy.

cacy of the combination of paclitaxel and cisplatin in DMPM. The rationale for using palcitaxel in this type of tumor is based on its demonstrated efficacy in animal experiments [18]. Paclitaxel was shown to inhibit the growth of 3 mesothelioma cell lines grown in the subcutaneous tissue of nude mice [18]. Though the numbers are too small to make meaningful conclusions, the response rate obtained with the combination of paclitaxel and cisplatin in our series (2/3) compares favorably with other chemotherapeutic regimens reported in these tumors.

Although the median survival of patients with DMPM reported in most series is short, occasional long-term survival has been described following intraperitoneal radioactive gold [19], intraperitoneal ^{32}P combined with whole abdominal radiation [20], and intraperitoneal chemotherapy [17]. Occasionally peritoneojugular venous shunting has provided symptomatic relief and long-term survival following chemotherapy [15].

Favorable prognostic variables among patients with mesotheliomas include young age, longer duration of symptoms, absence of pain, epithelial histologic type, good performance status, response to chemotherapy, extensive surgery, and combined surgery with chemotherapy [5,21–23].

Our series demonstrated a potential role for the tumor marker CA-125 in women with DMPM. Preoperative CA-125 values were elevated in 4 patients in whom the test was performed. To our knowledge, this has not been previously reported.

The current study demonstrates a potential benefit from surgical cytoreduction and combination chemotherapy, especially with paclitaxel and cisplatin. This is in agreement with previous reports which indicated that patients who had surgical resection combined with chemotherapy or radiation survived longer than those who had chemotherapy or radiation but no surgical resection [5,24]. Other studies demonstrated that intensive multimodality therapy increased survival among patients with DMPM compared with single modality therapy [21,22, 24,25].

CONCLUSIONS

DMPM are rare tumors with unfavorable prognosis that could be misdiagnosed as ovarian or primary peritoneal carcinoma in women. Pathologic diagnosis is often difficult and relies on immunohistochemical tests and electron microscopy. Surgical cytoreduction and multimodality therapy especially with paclitaxel and cisplatin chemotherapy might improve survival in this group of women.

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